

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Thorsten Bechert et al.
Serial No.: 10/570,230 Art Unit: 1618
File Date: August 17, 2006
Title BODY CARE PRODUCT CONTAINING POROUS SILVER PARTICLES
Examiner: Jake Minh Vu
Confirmation No.: 7580
Docket No.: WFG-39710

DECLARATION

I, Peter Steinrücke, hereby declare as follows:

1) I am a citizen of Germany residing at Im Posthof 1, 90461 Nürnberg, Germany.

I studied biochemistry in Hanover, Germany with a focus on microbiology and biophysical chemistry and earned my Diploma Biochemist. I earned by Doctorate Degree at the University of Lubeck (Germany) with completion of my thesis on bacterial electron transport of proteins and the genetics of cellular respiration. I continued to tutor and do post doctorate work at the university and was awarded the Otto Roth Price Award (1992), University of Lubeck.

I worked in the Molecular Biology Department as a post doctorate and group leader from 1992 to 2000 in the Leibniz Institute for Molecular Biotechnology in Jena, today the Fritz Lipman Institute of Germany. During this time period, my field of work included enzyme technology, molecular tools for biosensors, molecularly design for the detection of biomolecules, design of bioassays using surface plasmon resonance spectroscopy, fluorescence spectroscopy and electrochemical methods, and assays for characterizing antimicrobial materials.

I co-founded with Dr. Thorsten Bechert, Bio-Gate GmbH, a related company of the assignee of the present application.

My continued work at Bio-Gate resulted in the development of a new antimicrobial detection method that is now known as Certica, QualiScreen. On behalf of Bio-Gate GmbH I have planned, effected and achieved accreditation of an independent test laboratory facility, QualityLabs BT GmbH that is an ISO accredited.

I continue as a principal in Bio-Gate GmbH and since 2006, I am head of Research and Development and Intellectual Property Management and serve as a member of the Executive Board.

2) I am a co-inventor in the referenced application as well as WO 02/17984 (US Patent 6,984,392). I am familiar with the referenced application and prior patent. I have reviewed the Office actions issued on the application and consulted with patent counsel regarding the same.

3) The claimed particles are especially effective as topical body care products and are claimed in combination with topical carriers to enable topical application to skin and/or mucosa to treat infection and/or inflammation.

4) An unexpected and important characteristic of the particles is that their size and construction inhibit particle penetration of the deeper layers of skin, and the particles tend to act on only the outer skin layer to thereby provide a purely topical treatment.

5) The claimed particles have a mean diameter of between from about 1 micron to about 100 microns, which is more than a 1000 fold bigger than nanoparticles, and a mean internal porosity of at least 65% which promotes adhesion to the skin that is superior to the skin adhesion provided by smooth particles.

6) The stratum corneum (SC) or top layer of the skin comprises about 20 - 200 outer cell layers of the epidermis. The cells are dead and filled with keratin (cell cement).

7) The stratum corneum layer of the skin is the first and most important barrier since it is the first line of defense against foreign bacteria.

8) In the following example, *in vivo* confocal microscopy is used to show that the claimed particles remain on the participant's skin surface and/or in the stratum corneum without further penetration to deeper skin layers. The particles are visible on the skin surface and within skin folds.

In this example, the following topical cream formulation was

prepared with the claimed silver particles and other ingredients that do not interfere with penetration. The formulation is set forth with the following INCI list.

Vaseline, white
Cetearylalcohol
Paraffin oil
Glycerol 85%
Prunus dulcis (sweet almond oil)
Silver (claimed silver paticles at 0.5%)
Zinc oxide
Tocopherol
Water

The foregoing topical skin cream containing 0.5% by weight of the claimed particles was applied to human skin with typical hand application at environmental room temperature conditions. Exhibit A comprises prints of microscopy photographs showing:

- Photographs (b) and (c) show the particles are visible on the skin surface within the skin folds and at the follicles of the stratum corneum immediately following application of the skin cream; and
- Photographs (d) and (e) show the particles remain on the surface and/or within the stratum corneum two hours after application. The test period is selected to allow sufficient time for any potential particle penetration of the skin to occur, but no particle penetration occurs during and following the test period.

9) In demonstration of the absence of skin penetration by the claimed silver particles, particle penetration of pig skin is evaluated using a Franz Diffusion Cell. Such a pig skin evaluation is indicative of human skin results.

In this example, skin creams formulated as in paragraph 8 but containing the claimed silver particles in weight % amounts of 1.5% and 0.5% were tested. Each of the skin creams was applied onto the skin sample on the donor side of the cell at a dosage of 20 mg/cm² and maintained at an operating temperature of 32.2 degrees C.

The skin area used for testing was 1 cm². Only intact pig skin samples with intact barrier function were used.

After a 24 hour test period, a receptor chamber on the opposite side of the pig skin sample was tested for silver content. In all cases, no penetration was indicated.

10) Successive tape stripping experiments are done to remove the layers of the stratum corneum stepwise in layers. The cell layers and the correlating attached silver particles or silver ions that reside therein are removed by the cellophane tape.

In order to evaluate long term use, test participants topically applied the claimed silver particles two times per day over a test period of four weeks using a formulation with 0.5% of claimed silver particles.

Thereafter, tape stripping of the test area was performed at environmental room temperature using adhesive cellophane tape to recover silver particles on the skin surface.

The result of the tape stripping shows that most of the silver particles are recovered from the outer skin layers of the stratum corneum. Taken together with the skin penetration test using the diffusion cell as reported in paragraph 9, one can say that therefore substantially all of the silver particles are recovered from the outer skin and the outer skin layers of the stratum corneum, and no penetration of the particles into deeper skin layer is indicated. The tape stripping also removes the stratum corneum together with silver particles contained within this skin layer. Substantially all of the applied silver particles are recovered and no penetration of the particles into deeper skin layers is indicated.

Test stripping showed that even under these conditions, the migration behavior from the outer surface into the stratum corneum deeper layers apparently was poor.

Resident microbial flora is not present on the outer skin surface alone, but in contrast to the transient flora, is also maintained in deeper zones of the stratum corneum and in the hair follicle sheats. In both of these areas, the claimed silver particles do not unfold their action. However,

considerably smaller particles, such as nanoparticles that are several orders of magnitude smaller, may have a much easier access and exert their effects. Other ingredients that even penetrate the skin transdermally should also affect the resident flora much stronger. It is believed that the higher tendency of the claimed particles to agglomerate with each other is advantageous to inhibit effects on resident flora in deeper zones of the stratum corneum and in the hair follicle sheaths. Such intertwined particles are even less probable to penetrate skin layers.

In comparison, the ongoing discussion about the biosafety of nanosilver preparations very often warns about the extremely small sizes of such particles. The fear is not only might they easier penetrate the skin but even the blood-brain-barrier could be affected. The claimed silver particles have such poor penetration properties that one can rule out all those anticipated risks which are associated with the application of nanosilver. It is also far easier to detect the claimed particles than to hunt for nanoparticles that are more like atom clusters. Irrespective what might be found out in the years to come for nanosilvers, one can declare today already there is no such risks for the claimed silver particles.

11) In contrast with the claimed particles, nanoparticles are acknowledged in the art to be taken up by animals and pass from the lung into the bloodstream. Brumfiel, G. Nature (2003) Vol. 424, pages 246 to 248, as cited at page 1 of the present application.

12) There is no unified regulatory approach for certification of cosmetic products including nanoparticles and such may only be acquired after new procedures are developed and the methods thereof validated to prove that nanoparticles are harmless even after extended use.

13) Accordingly, it is an unexpected and most valuable feature of the claimed particles that they are primarily retained on the skin surface and in the top layers of the stratum corneum so as to not affect the normal skin flora residing in the lower layers of the stratum corneum.

14) Further, it was not expected that the claimed particles would provide the necessary silver ion concentration for effective antimicrobial treatment at the low dosages used in the tested topical medicaments. The latter is believed to be associated with the porosity resulting from the size and construction of the particles. More particularly, the particle size gives rise to a tendency for the particles to be retained at the skin surface with porosity enhanced ion

delivery so as to improve the local silver ion availability in accordance with topical treatment.

Therefore, the innovative approach was to have a microstructure to avoid the nanosilver and at the same time to have a porosity enhanced ion availability and an antimicrobial effect that is more focused to the skin surface than with smaller more compact nanoparticles that lack such preferential skin location and also the concomitant porosity. There is not a complete loss of antimicrobial efficacy if you reduce the preference for skin surface location and/or the porosity structure. But in terms of safety issues and biocompatibility, it is better to have the claimed silver particles that stay mainly on top of the skin.

15) In the absence of the unique and unexpected properties of the claimed particles as taught in the present application, it would not be expected or obvious for one skilled in the art to use the corresponding particles in a topical cream based on the teachings in the prior patent WO 02/17984 (US Patent 6,984,392). The patent discloses the use of the particles with inanimate objects and never suggests topical application for skin and/or mucosa contact. This is also true since the particles per se are difficult and expensive to produce so as to not suggest and, in fact, negate their use in a topical cream application. The mere antimicrobial effects of silver do not overcome the lack of teachings in Bechert and adverse practical considerations negating the use of such particles in a topical skin cream.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Türrberg
Place of Execution

May 23rd 2011
Date of Execution

Peter Steinrücke